PATENT NO EP(UK) .....0155057.....

TRANSLATION OF EUROPEAN PATENT (UK) UNDER SECTION 77(6) (a)

Date of Publication of the Translation ....24.....MAY 1989

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1. European Patent Number: 0158057

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3. European Patent Bulletin Date:

26 04 89
Day Month Year

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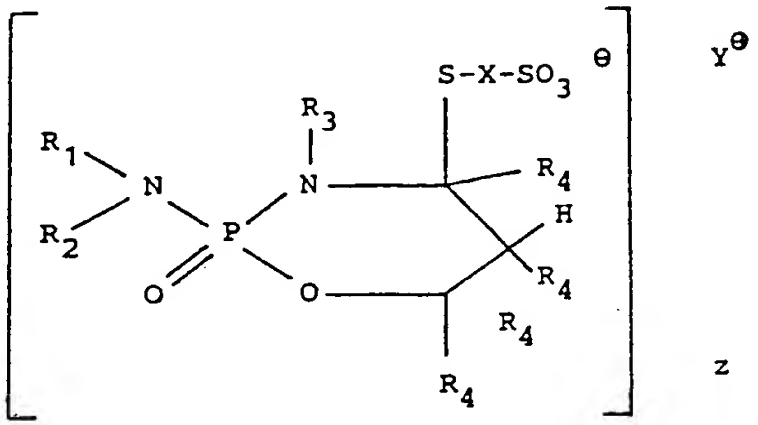
I, WOLFGANG GERSON BARB, B.Sc., Ph.D., F.P.R.I., F.I.L., of "Spring Wood", Hedgerley Lane, Gerrards Cross, Bucks., declare that I am conversant with the German and English languages and that to the best of my knowledge and belief the accompanying document is a true translation of the text on which the European Patent Office intends to grant or has granted European Patent No. 0,158,057 in the name of ASTA Pharma AG

Signed this 5th day of April 1989

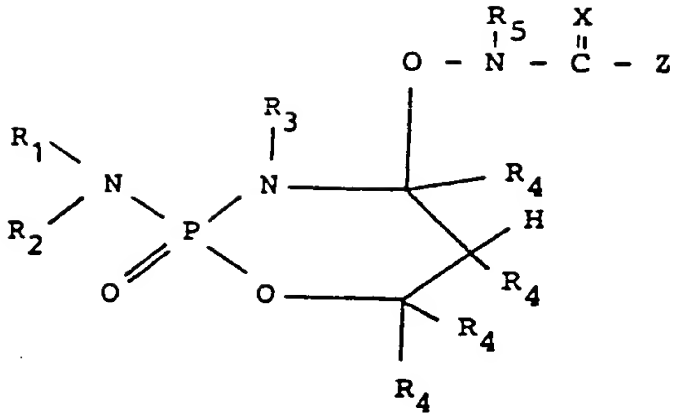
W.G. BARB

In Belgian Patent 892,589, oxazaphosphorine-4-thioalkanesulphonic acids and certain salts thereof of the general formula



are described. In the preceding formula:
R_1, R_2 and R_3, which can be identical or different from one another, denote hydrogen, methyl, ethyl, 2-chloroethyl or 2-methanesulphonyloxyethyl, where at least two of these radicals are 2-chloroethyl and/or 2-methanesulphonyloxyethyl,
R_4 denotes hydrogen or methyl,
X denotes a straight or branched-chain C_{2-6}-alkylene which can have a mercapto group on the carbon atom of the alkylene chain in the 1, 2, 3, 4 or 5 position, and
$Y^{\oplus}$ denotes the hydrogen cation, an alkali metal cation or an alkaline earth metal cation, the guanidinium, morpholinium or cyclohexylammonium cation or the cation which is derived from an amine of the formula $NR_5R_6R_7$, wherein the radicals R_5 to R_7 are identical or different and denote hydrogen, C_1-C_2-alkyl groups or oxyethyl groups, or $Y^{\oplus}$ is the ethylenediammonium cation $H_3\overset{\oplus}{N}-CH_2CH_2-\overset{\oplus}{N}H_3$ or the piperazinonium cation and z is 1 when $Y^{\oplus}$ is a monobasic cation, or z is 2 when $Y^{\oplus}$ is a dibasic cation or the cation of a compound containing two monobasic cations.

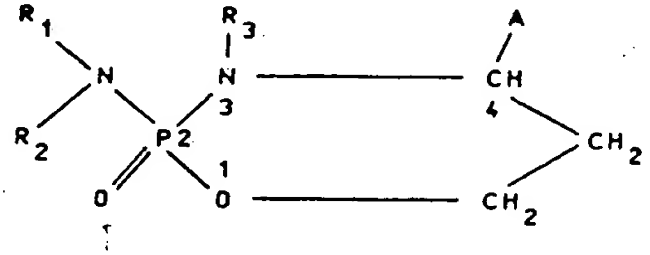
Furthermore, German Offenlegungsschrift 3,133,309 relates to 4-carbamoyloxyoxazaphosphorine derivatives of the general formula



wherein X is sulphur or oxygen, R_1, R_2 and R_3, which can be identical or different from one another, represent hydrogen, methyl, ethyl, 2-chloroethyl or 2-methanesulphonyloxyethyl, the radicals R_4, which can be identical or different from one another, represent hydrogen, methyl or ethyl, R_5 is hydrogen, C_{1-4}-alkyl, hydroxy-C_{1-4}-alkyl or phenyl, and Z, inter alia, is also a C_1-C_{18}-alkylamino group which can contain various substituents, among them also the carboxyl group, and their pharmaceutically utilizable salts. A compound is described as an example in this DE-OS, wherein Z is the group $-NH-CH_2-CO_2H$ and the corresponding cyclohexylamine salt.

The compound (sic) of Belgian Patent 892,589 and German Offenlegungsschrift 3,133,309 possess anti-tumour action and also an immunosuppressive action.

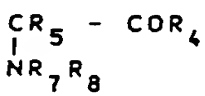
The invention relates to salts of oxazaphosphorine derivatives of the general formula



I

wherein R_1, R_2 and R_3, which can be identical or different from one another, represent hydrogen, methyl, ethyl, 2-chloroethyl or 2-methanesulphonyloxyethyl and in this case at least two of these radicals are 2-chloroethyl

and/or 2-methanesulphonyloxyethyl and A is the group $-S-alk-SO_3H$ or $-N(OH)-CONH-alk-CO_2H$ and alk represents a C_2-C_6-alkylene radical optionally containing a mercapto group, where alk can also be $-CH_2-$ if the carboxyl group is on the group alk,
with homocysteine thiolactone or α-amino-ε-caprolactam or a basic compound of the formula

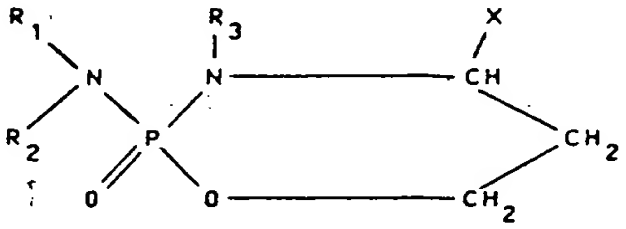


II

wherein R_4 is a hydroxyl group, an amino group or a C_1-C_6-alkoxy group, R_5 is hydrogen or a difluoromethyl group, R_6 denotes hydrogen, a 3-indolylmethyl radical, a 4-imidazolylmethyl radical, a C_1-C_{10}-alkyl group or a C_1-C_{10}-alkyl group which is substituted by a hydroxyl group, a C_1-C_6-alkoxy group, a mercapto group, a C_1-C_6-alkylthio group, a phenyl group, a hydroxyphenyl group, an amino-C_1-C_6-alkylthio group, an amino-C_1-C_6-alkyloxy group, an amino group, an aminocarbonyl group, a ureido group ($H_2NCONH-$), a guanidino group or a C_1-C_6-alkoxy-carbonyl group, or wherein R_6 together with the structural moiety $>CR_5(NR_7R_8)$ forms the proline radical, the 4-hydroxy-proline radical or the 2-oxo-3-amino-3-difluoromethylpiperidine and the radicals R_7 and R_8 represent hydrogen or C_1-C_6-alkyl radicals.

The invention furthermore relates to a process for the preparation of salts of oxazaphosphorine derivatives of the previously indicated formula I, which is characterized in that

a) a compound of the general formula



III

wherein X is a hydroxyl group or a C_1-C_4-alkoxy group, is reacted with the salt of the compound

AH

IV

wherein A has the meanings indicated and the basic salt component is homocysteine thiolactone, α-amino-ε-caprolactam or the basic compound of the formula II having the meanings indicated for the radicals R_4 to R_8, or is reacted first with the compound AH and subsequently with the previously mentioned basic compounds, or a compound of the general formula (III), wherein X is a C_1-C_{10}-alkylthio group which is optionally substituted by a carboxyl group, a hydroxyl group or a C_1-C_4-carbalkoxy group, a benzylthio group or a C_1-C_6-alkanoylthio group, or wherein X represents the group -N(OH)-CO-NHR and R denotes hydrogen, a C_1-C_6-alkyl group, a benzyl group or a phenyl group which is optionally substituted by C_1-C_4-alkyl radicals or halogen, or wherein X is the group A and the radical X can also be present in the salt form, is reacted with excess of a compound of the formula

A'H V

or a salt of this compound A'H or with homocysteine thiolactone, α-amino-ε-caprolactam or the basic compound of the formula II having the meanings indicated for the radicals R_4 to R_8, where A' is different from A and has one of the meanings indicated for A or

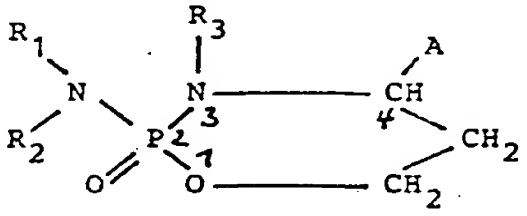
b) a compound of the formula I or the salt of a compound of the general formula I is reacted with homocysteine thiolactone, α-amino-ε-caprolactam or a basic compound of the formula II having the meanings indicated for R_4 to R_8 or with its salts with the formation of the corresponding salts

and optionally exchanging the basic component or the acidic hydrogen of the group A, if this is not present as a salt, for another basic compound in the context of the definition given therefor in the compounds obtained.

The compounds according to the invention have strong antitumour activity and can be used in particular for combating cancer. Compared to the previously known compounds of Belgian Patent 892,589 and German Offenlegungsschrift 3,133,309, they possess, for example, a reduced toxicity (for example reduced acute toxicity and

leucotoxic action) and therefore exhibit an improved therapeutic index and a better local and systemic and also venous tolerability. Furthermore, the compounds according to the invention possess a reduced immunosuppressive action, a reduced local tissue irritation and, frequently, lower haemolytic action. Moreover, the compounds according to the invention possess no or only low circulatory side effects (for example sympathomimetic actions). The blood pressure is also less disruptively influenced.

The compounds of the formula I have the following structure:



wherein R_1, R_2, R_3 and A have the meanings indicated therefor. Claim 1 relates to the salts of such compounds of the formula I with homocysteine thiolactone or α-amino-ε-caprolactam or a compound of the formula II.

The alkylene radical (alk) of the formula I can be straight or branched. Examples thereof are methylene, dimethylene, trimethylene, tetramethylene, pentamethylene or hexamethylene radicals or, for example, the radicals $-\underset{\underset{CH_3}{|}}{CH}-CH_2-$, $-\underset{\underset{CH_3}{|}}{CH}-(CH_2)_2-$, $-C(CH_3)_2-CH_2-$ or $-CH_2-\underset{\underset{CH_3}{|}}{CH}-CH_2-$; in particular the chain alk consists of 2 or 3 C-atoms, if it is unbranched. If alk is branched, the part which is bonded to the acid group and to the sulphur or nitrogen atom consists in particular of 2 or 3 C-atoms. If the carboxyl group is on the group alk, alk is preferably $-CH_2-$. If the radical alk contains a mercapto group (this can in particular be the case if it is the -S-alk-SO_3H group), this mercapto can be placed on the carbon atom in the 1, 2, 3, 4 or 5 position. The numbering begins with the C-atom on which the acid group, for example the $-SO_3H$ group, is. In particular, in this case it is the

$-CH_2-CH(SH)-CH_2$ radical.

Preferably, those compounds are suitable where R_3 is hydrogen, R_1 and R_2 are each 2-chloroethyl and A is the group $-S-CH_2-CH_2-SO_3H$ or $-N(OH)-CO-NH-CH_2-CO_2H$.

The alkyl groups, alkoxy groups or alkylthio groups occurring in the formula II can be straight or branched. The C_1-C_{10}-alkyl group preferably contains 1-6 carbon atoms. In the alkoxy groups and alkylthio groups it is preferably those having 1-4, in particular 1-2 C-atoms; this applies with respect to the radicals R_7 and R^8, if these are alkyl radicals. If, in the formula II, R_6 is an alkyl group which contains an amino-C_1-C_6-alkylthio-(C_1-C_6-alkoxy) group, then it is preferably the following groups: $H_2N-CH_2-CH_2-S-CH_2-$ or $H_2N-CH_2-CH_2-O-CH_2-$.

In the compounds of the formula II, it is preferably those compounds where R_4 is a hydroxyl group and the radicals R_5, R_7 and R_8 are hydrogen and R_6 can in particular assume the meanings which are indicated for this in the following. Preferred basic compounds of the formula II are, for example, those where R_4 denotes a hydroxyl group, R_5 denotes hydrogen or difluoromethyl, R_6 denotes a C_1-C_{10}-alkyl group, in particular a C_1-C_6-alkyl group which contains (preferably in the 2, 3, 4, 5 or 6 position; numbering always begins on the bonding site of the alkyl radical with the rest of the molecule) an amino group (in particular in the 3 or 4 position), an amino-C_2-C_4-alkylthio group, an amino-C_2-C_4-alkoxy group, a guanidino radical, a 4-imidazolylmethyl radical or a 3-indolylmethyl radical and R_7 and R_8 denote hydrogen or C_1-C_4-alkyl radicals; or amino acid derivatives of the formula II where R_4 denotes an amino group or a C_1-C_4-alkoxy group, R_5 denotes hydrogen, R_6 denotes hydrogen, a phenylmethyl group, a 4-hydroxyphenylmethyl group or a C_1-C_6-alkyl group which contains (preferably in the 2, 3, 4, 5 or 6 position) a hydroxyl group, a mercapto group, a C_1-C_4-alkylthio group, an aminocarbonyl group, a C_1-C_4-alkoxycarbonyl group or a ureido group and R_7 and R_8 denote hydrogen or C_1-C_4-alkyl radicals.

In the previously mentioned amino acids or amino acid derivatives, the salts are each formed, for example, from one mole of oxazaphosphorine I and one mole of the compound II.

Furthermore, suitable basic compounds of the formula II are, for example, those where R_4 is an amino group or a C_1-C_4-alkoxy group, R_5 denotes hydrogen or difluoromethyl, R_6 denotes a C_1-C_{10}-alkyl group, in particular a C_1-C_6-alkyl group which contains (preferably in the 2, 3, 4 or ω position) an amino group, an amino-C_2-C_4-alkylthio group, an amino-C_2-C_4-alkoxy group, a guanidino radical, a 4-imidazolylmethyl radical or a 3-indolylmethyl radical and R_7 and R_8 denote hydrogen or C_1-C_4-alkyl radicals. In the last-mentioned amino acid derivatives, the salts are each formed, for example, from 2 moles of oxazaphosphorine and 1 mole of the amino acid derivative of the formula II.

Individual examples of compounds of the formula II are: aspartic acid diamide (DL-form), diethyl aspartate (L-form), citrullinamide (H_2N-CO-NH-$(CH_2)_3$-$CH(NH_2)$-$CONH_2$, L-form), ornithine ethyl ester (L-form), arginine, arginamide (L-form), 4-thialysine (H_2N-CH_2-CH_2-S-CH_2-$CH(NH_2)$-COOH), 2,6-diaminooenanthic acid (ε-methyllysine), 4-oxalysine (H_2N-CH_2CH_2-O-CH_2-$CH(NH_2)$-COOH), glycinamide, N,N-dimethylglycinamide and the corresponding methyl or ethyl esters, prolinamide, hydroxyprolinamide, phenylalaninamide, the methyl or ethyl ester of alanine or phenylalanine, homocysteine thiolactone (DL-form), αamino-ε-caprolactam (D(+)-form), lysine (in particular L-lysine), difluoromethylornithine (DL- or L-form), valine methyl ester (L-form), threonine ethyl ester, histidine methyl ester, histidinamide, alaninamide or ornithine.

In the salts according to the invention, for the case in which R_4 is an amino group or an alkoxy group in the compound II, and otherwise no basic group is present, or for the case in which R_4 is the hydroxyl group and otherwise only one basic group is present, compound I (acid component) and compound II (basic component) are

present practically in the ratio 1:1. (This also applies if the basic component is homocysteine thiolactone or α-amino-ε-caprolactam). If, on the other hand, R_4 is an amino group or an alkoxy group in the basic component II and if this still contains an additional basic group in addition to the amino group in the α position, then the ratio of compound I to compound II is in general 2:1. The salts according to the invention are the neutral salts. In the case of the sulphonic acid salts, they have, for example, pH values between 3.5-6. If they are the carboxylic acid salts, the pH values are, for example, between 6-9, in particular 6-8.

For process a)

The process is carried out in a solvent at temperatures between -60°C and +90°C, preferably -30°C to +60°C, in particular -20 to +30°C, i.e. optionally with cooling, at room temperature or with warming. The reaction can be carried out in the presence of an acidic catalyst, such as an inorganic or organic acid such as, for example, trichloroacetic acid, p-toluenesulphonic acid, trifluoromethanesulphonic acid or a Lewis acid such as $AlCl_3$, $ZnCl_2$, $TiCl_4$ or boron trifluoride etherate. For the reaction, for example, a pH between 1 and 8, preferably between 2 and 6, is set. This applies in particular when the starting components are employed as salts, and optionally also when the free acids are employed and A in particular contains the carboxyl group. Possible solvents are, for example:

water, alcohols, in particular alkanols having 1-6 C-atoms such as methanol, ethanol, propanol or isobutanol, alkyl ketones each having 1-4 C-atoms such as, in particular, acetone, methyl ethyl ketone, aprotic solvents (for example dimethyl sulphoxide, acetonitrile, N-methylpyrrolidone, dimethylformamide, hexamethylphosphoric triamide), halogenated hydrocarbons having 1-3 C-atoms such as chloroform, ethylene dichloride, saturated cyclic ethers such as tetrahydrofuran, dioxane, saturated lower aliphatic ethers such as diethyl ether or similar solvents or mixtures of several such solvents.

If the symbol X in the starting compound III is the hydroxyl or alkoxy group, the reaction can also take place in 2 steps by reacting, for example, the compound III first with the compound AH (without acidifying) and subsequently adding the basic component II or homocysteine thiolactone or α-amino-ε-caprolactam to the reaction mixture in a solvent, optionally after evaporation and addition of another possible solvent.

The use of a compound III, wherein X is the hydroxyl group or an alkoxy group, is particularly suitable if the final product is produced as crystals.

If X is not hydroxyl or alkoxy, or if X is present in the salt form, the compound A'H or its salt are employed in excess, for example 1.5-10 moles, preferably 2-5 moles of the compound A'H or its salt per mole of the compound III. The pH value of the reaction solution is adjusted, for example, to 5.5-9, preferably 6.5-8 by means of alkaline liquor or using an amine (expediently the amine which is already present in the employed salt as a basic component); under certain circumstances, a pH value up to 12 can also be favourable. This applies in particular when the starting components are employed as salts, optionally also when the free acids are employed and A in particular contains the carboxyl group. The reaction temperature is, for example, 10-90°C, preferably 25-60°C. The reaction time is, for example, several seconds up to several hours. Subsequently, for example, the reaction solution is cooled to under 10°C and brought using a mineral acid (H_2SO_4, HCl, phosphoric acid), a sulphonic acid (for example mercapto-C_1-C_6-alkanesulphonic acid) or an ion exchanger (H^+-form) to a pH between 4 to 5.5 or even7. The isolation of the process products can, for example, take place: by crystallization or by a chromatographic process, in particular by preparative high pressure liquid chromatography, optionally again using subsequent reaction in the desired salt form on a suitably loaded cation exchanger.

If X in the formula III is the group A and this is present in the salt form, those salts, for example,

are suitable which are described in German Offenlegungsschrift 3,133,309 or Belgian Patent 892,589. For example, the ammonium salts, cyclohexylammonium salts or guanidinium salts are suitable. Of course, other customary salts can also be employed, for example optically active bases which are customary for cleavage of racemates, which can be prepared analogously to the methods described there.

The starting materials of the formula III are, for example, known from the following literature sources or can be obtained analogously to the methods described there: Belgian Patent 892,589, German Offenlegungsschrift 3,133,309, Tetrahedron Letters No. 10 (1979), pages 883-886, Cancer Treatment Reports, Volume 60, No. 4 (1976), pages 429-435. If X is an optionally substituted C_1-C_{10}-alkylthio group, those compounds of the formula III are in particular suitable where X is a C_1-C_6-alkylthio group, the group $-S-(CH_2)_n-CO_2H$ (n = 1-6, in particular 1-3), $-S-(CH_2)_n-OH$ (n = 2-6, in particular 2-4) or $-S-(CH_2)_n-CO-OC_2H_5$ (n = 1-6, in particular 1-3). If X is a C_1-C_6-alkanoylthio group, it is in particular the acetylthio group. If X is the group -N(OH)-CO-NHR and R is a C_1-C_6-alkyl group (straight or branched), these particularly consist of 1-4, preferably 1-2 C-atoms.

The preparation of the starting salts AH of the formula IV or the starting salts A'H of the formula V can take place with or without solvent at temperatures between 0 and 40°C by reaction of a compound AH or A'H with a basic compound or homocysteine thiolactone or α-amino-ε-caprolactam or a compound of the formula II. Suitable solvents are, for example: water, C_1-C_6-alkanols (methanol, ethanol), lower aliphatic ketones (acetone), cyclic ethers (dioxane), chlorinated hydrocarbons (methylene chloride, ethylene dichloride, chloroform, carbon tetrachloride), saturated lower aliphatic ethers (diethyl ether), aprotic solvents (for example dimethylformamide, dimethyl sulphoxide, acetonitrile) or mixtures of these agents.

The preparation of salts of this type can take

place, for example, by dissolving an alkali metal salt (sodium salt) of the acid AH or A'H in water (for example 1 to 20% solution; % = per cent by weight) allowing this solution to pass through a column containing a strong acidic ion exchanger (H^+-form, 3-fold excess) and neutralizing the free acid in the eluate with the basic component, concentrating in vacuo and optionally recrystallizing the residue using a lower alcohol (methanol, ethanol), a lower ketone (acetone) or an ether (diethyl ether).

For process b)

This process is carried out at temperatures between 0-25°C, preferably 0-5°C. Possible solvents for this process are, for example: water, lower aliphatic alcohols, lower aliphatic ketones or mixtures of these agents. 1 mole of the component I is reacted with 1 mole of the component II. It is expedient to work in a pH range between 3 to 8. Using compounds I, wherein A is the S-alk-SO_3 group (or a salt thereof), the reaction is preferably carried out at a pH between 3-6, preferably 3.8-5, in particular pH 4; using compounds I, wherein A is the -N(OH)-CO-NH-alk-CO_2H group (or a salt thereof), the reaction is preferably carried out at pH values between 6-8, preferably pH 7.

Frequently, the addition of a buffer is favourable. Possible buffer systems having a pH range between 3.8 to 5.0 are, for example: citric acid/sodium citrate; acetic acid/sodium acetate; phosphoric acid/sodium dihydrogen phosphate; tartaric acid/sodium tartrate; formic acid/sodium formate; sodium (sic) hydrogen phosphate/citric acid; succinic acid/sodium succinate; propionic acid/sodium propionate; aconitic acid/sodium aconitate; β,β-dimethylglutaric acid and its sodium salt; maleic acid/sodium maleate; compound II/citric acid. Suitable buffers for a pH range of 6 to 8 are, for example: Na citrate/NaOH, tris-(hydroxymethyl)aminomethane maleate/NaOH, KH_2PO_4/NaOH, KH_2PO_4/Na_2HPO_4.

For the preparation of the buffer, homocysteine thiolactone or α-amino-ε-caprolactam or a basic compound

of the formula II can also be used instead of the sodium hydroxide solution so that the buffer already contains the basic component which is also present in the final product of the formula I.

The exchange of the basic component of a salt of the compound I with a basic component according to the invention can take place, for example, on acidic ion exchangers which are loaded with homocysteine thiolactone, α-amino-ε-caprolactam or the basic compound II. In this case, the basic compound II (which is now bonded to the acidic groups of the ion exchanger) is employed in excess (for example 2 to 10 moles, preferably 5 moles of the component II to 1 mole of the component I). Suitable acidic ion exchangers are, for example, those whose polymeric matrix can carry sulphonic acid groups or carboxylic acid groups. The matrix of the ion exchanger can, for example, consist of a polystyrene resin optionally containing 2 to 16, preferably 4 to 8 of divinylbenzene or even a phenol resin. The polystyrene ion exchanger is preferably a gel. The loading of the ion exchanger with the basic component can take place, for example, in the following manner: 150 ml of ion exchange resin of 1.2 mval/ml*) in a column (diameter about 4 cm) having a cooling jacket are regenerated with hydrochloric acid and washed neutral and free of chloride ions using distilled water. Subsequently, the exchanger is treated with a 10% strength aqueous solution of the basic compound (220 mmol) and washed neutral with distilled water. Additionally, ion exchangers containing a buffer (citric acid/citrate or acetic acid/acetate) of about pH 4 can be treated and the buffer can subsequently be washed out again. In addition, the ion exchanger can also be loaded using neutral amino acid salts of the formula II or neutral salts of homocysteine thiolactone or α-amino-ε-caprolactam (for example hydrochlorides or hydrobromides).

*The manufacturer of the ion exchanger states the capacity of the ion exchanger (i.e. the amount of functional groups such as $-SO_3H$, $-CO_2H$) in mval/ml or mval/g of the ion exchange resin.

If ion exchangers are used, it is favourable to add the buffer to the receiver for the eluate. In some cases, the joint elution of the salt with the buffer and/or the salt of a mercapto-C_2-C_6-alkanesulphonic acid through the ion exchanger is advantageous. Similarly, the joint elution of the salt with only the buffer is also possible. For example, the starting compound, i.e. the compound I (A = -S-alk-SO_3H) or a customary known salt of the compound I is dissolved in a buffer at pH 3.8 to 5.0, preferably pH 4.1, and this solution is added above the ion exchange column and the eluate is also collected in a suitable buffer solution. The eluate or the lyophilizate prepared therefrom then consists, for example, of the salt according to the invention and the buffer and/or the salt of the mercaptoalkanesulphonic acid, or of the salt according to the invention and only the buffer. Preferably, the eluate, optionally after dilution with water, is in each case immediately frozen or lyophilized. If the symbol A is the group -N(OH)-CO-NH-alk-CO_2H in the starting compound I, the reaction is expediently carried out analogously, but now at pH values between 6-8 (for example pH 7).

In this case, however, the reaction can also be carried out in such a way that a customary salt of the compound I (for example an alkali metal salt) is allowed to pass in aqueous solution through an acidic ion exchanger as mentioned above in the H^+-form and the compound I is then neutralized in the eluate with the basic component of the formula II or with homocysteine thiolactone or α-amino-ε-caprolactam. This process possibility is particularly suitable when the final product is produced as crystals.

Suitable starting salts of the compound of the formula I are, for example, those which are described in German Offenlegungsschrift 3,133,309 or Belgian Patent 892,589. For example, the ammonium salts, cyclohexylammonium salts or guanidinium salts are suitable. However, other customary salts (for example salts with optically active bases which are customary for racemate

cleavage) can also be employed, which can be prepared analogously to the methods described there.

The oxazaphosphorine derivatives of the formula I according to the invention are taken to mean all possible stereoisomers and mixtures thereof. In detail, these are, for example, cis/trans-isomers, i.e. the cis- or trans-position of the group A to the oxo atom in the 2 position (phosphoryl oxygen) to the plane of the oxazaphosphorine ring. These are thus, for example, cis-isomers and the trans-isomers (in each case the racemate and the corresponding enantiomer), the separated cis-isomers and the separated trans-isomers. Diastereomeric salts (for example when a chiral amine is used for salt formation), can be separated in a known manner, preferably by fractional crystallization. The pure enantiomers can also be obtained by the customary methods for racemate cleavage, for example by fractional crystallization of the diastereomeric salts from racemic acids of the formula I and optically active bases or optionally by the use of optically active starting products according to formula III in the synthesis.

In general, cis/trans-mixtures can be formed in the synthesis. In general, mixtures are formed which predominantly consist of the cis-isomers and to about 5-10% of the trans-isomers. The compounds according to Examples 1-5 consist, for example, of the cis-isomers containing less than 5-10% of the trans-form.

With well-crystallizing compounds, the cis- or the trans-form, in particular the cis-form, is obtained crystallized from such mixtures. If, however, the reaction is carried out in anhydrous solvents or in solvents having low water content, a single form, in particular the cis-form, is obtained exclusively or very predominantly. Thus the pure cis-form of a non or poorly crystallizing compound according to formula I can, for example, be prepared by adding an acetone solution of the compound according to formula III to an aqueous solution of the compound according to formula IV or its salts at temperatures between -30 and +20°C and, after completion of the

reaction, dissolving and reprecipitating several times.

The starting compounds according to formula III can be employed as racemic cis- and trans-isomers (for preparation see the previous page), as the optically active cis- and trans-form and as mixtures thereof (for this see Belgian Patent 892,589 and German Offenlegungsschrift 3,133,309, page 12).

For racemate cleavage, for example, suitable optically active bases are, for example, 1-phenylethylamine, brucine, quinidine, strychnine and cinchonine and also additional bases and methods which are described in "Optical Resolution Procedures for Chemical Compounds", Vol. 2, Paul Newman, 1981, Publishers Optical Resolution Information Center in Riverdale, USA. For this, for example, a racemic salt according to the invention is converted in the already indicated manner into a salt with one of the previously mentioned optically active bases, the enantiomers are separated in a known manner and the optically active base of the enantiomers thus obtained is then replaced again by a basic compound according to the invention. The previously mentioned optically active bases can, however, also be employed in the synthesis in process a) in the reaction of a compound of the formula III with a compound of the formula IV or V or in process b) as the basic salt component. In this case, this optically active base is subsequently exchanged in a customary manner with the basic salt component according to the invention corresponding to the already indicated definition.

The basic salt components according to the invention homocysteine thiolactone, α-amino-ε-caprolactam and the compounds of the formula II are possible as racemates or in the form of the pure enantiomers.

In general, the L-forms are preferred.

The salts according to the invention are taken to mean all forms which result from the different asymmetric carbon atoms present, i.e. for example racemates, optically active forms or diastereomeric forms.

In the preparation, it is only recommended to

keep the salts according to the invention in solution for as short a time as possible in order to prevent or to keep as low as possible hydrolysis to the 4-hydroxyoxazaphosphorines and/or epimerization on the C-4-atom of the oxazaphosphorine ring (conversion of the cis-form into the trans-form). If the salts according to the invention are strongly contaminated (for example contain greater amounts of starting compounds), they can be obtained in pure form by customary chromatographic methods (in particular by preparative high pressure liquid chromatography).

The salts according to the invention are stable, can be stored (in particular at 4°C) and can be administered well pharmaceutically. For pharmaceutical preparations (for example injection solutions or lyophilizates which are stable to hydrolysis), in particular also with regard to the stability in storage, it is recommended to set a pH range of about 3.5-7 in the sulphonic acid derivatives with the aid of a customary buffer (for example citrate buffer). The pH optimum in this case is pH 4.0-4.3. For the case in which the radical A is derived from the group $-N(OH)-CO-NH-alk-CO_2H$, a pH of 6.5-7.5 is expediently set. These pH value settings can be carried out both for solutions and suspensions and for solid pharmaceutical preparations.

Moreover, depending on the addition of a buffer, the addition of 0.5 to 5 equivalents of a salt (for example an alkali metal salt, in particular a sodium salt) of a mercapto-C_2-C_6-alkylsulphonic acid (for example a salt of 2-mercaptoethanesulphonic acid) and its disulphide and additional thiols (for example cysteine) is also advantageous. The type of thiols and disulphides and the mode of their use are described in European Patent Application 83,439. Suitable salts of this type are, for example, the alkali metal salts (Na, K) or the salts with a basic component according to the invention (compound of the formula II, homocysteine thiolactone, α-amino-ε-caprolactam). The addition of the salt of a mercapto-C_2-C_6-alkanesulphonic acid can take place, for example, by addition of an aqueous solution of the

sulphonic salt (alkali metal salt, for example 20 per cent by weight) to an aqueous solution of the salt according to the invention (preferably buffered at a pH between 4 and 4.3). The mixture thus obtained is then, for example, lyophilized.

The advantages in the addition of a mercapto-alkanesulphonic acid salt thereby consist in the following: improvement of the stability in storage and also the stability in aqueous solution in the salts according to the invention. (This is, for example, of significance in the preparation of the salts but also in dissolving, for example, lyophilizates before use); improvement in the chemotherapy of cancers by means of the salts according to the invention, in particular with respect to toxic side effects (compare European Patent Application 83,439, European Patent 2,495, German Patent 2,806,866).

The salts according to the invention are suitable for the preparation of pharmaceutical compositions or preparations. The pharmaceutical compositions or medicaments contain one or more of the salts according to the invention as active compounds, optionally mixed with other pharmacologically or pharmaceutically active substances. The preparation of the medicaments may take place using the known and customary pharmaceutical excipients and auxiliaries.

The medicaments may be used, for example, enterally, parenterally, orally, perlingually or in the form of sprays. Administration may take place, for example, in the form of tablets, capsules, pills, coated tablets, suppositories, liquids or aerosols. Suitable liquids are, for example: oily or aqueous solutions or suspensions, emulsions, or injectable aqueous or oily solutions or suspensions.

On intravenous, intraperitoneal or oral application, the compounds according to the invention show good cytostatic and curative activity in various experimental tumours of the rat and the mouse. For example, the compounds according to the invention are intraperitoneally or orally administered to the rat using different doses

5 days after intraperitoneal implantation of 10^5 cells of leukaemia L5222 and, depending on the dose, a curative action is obtained. The recurrence- and metastasis-free survival of the tumour-carrying animals after 90 days is defined as a cure. From the frequency of cures obtained using the various doses, that dose with which 50% of the tumour-carrying animals can be cured is calculated as the mean curative dose (DC50) by means of probit analysis according to R. Fisher.

For example, the compounds according to the invention are administered intravenously, intraperitoneally or orally using various doses even one day after intraperitoneal implantation of 10^6 cells of the Yoshida ascites sarcoma AH13 and, depending on the dose, a curative action is obtained. Here also, the curative action is defined as the recurrence- and metastasis-free survival of the tumour-carrying animals over 90 days.

In a corresponding manner, that dose with which 50% of the tumour-carrying animals can be cured is calculated as the mean curative dose (DC50) by means of probit analysis according to R. Fisher.

Furthermore, the compounds according to the invention are, for example, administered intravenously, intraperitoneally or orally using various doses once daily or several times daily (4 x) on successive days after intraperitoneal implantation of 10^6 cells of mouse leukaemia L1210 and a cytostatic action is obtained. The cytostatic activity can be detected as the lengthening of the median survival time of the tumour animals and is expressed as the dose-dependent percentage lengthening of the survival time compared to an untreated control group. With the rat tumours, the mean curative dose, depending on the administration form, is in the range from 0.1-10 mg/kg. With the same doses, a lengthening of the median survival time of 100% can be obtained in mouse leukaemia L1210.

Moreover, the compounds according to the invention stimulate antibody production in a determined low dose range. This dose range is, for example, between 20-50 mg/kg per rat (intravenously, intraperitoneally) for the com-

pound according to Example 5. On the other hand, the antibody production by the known antitumour agent cyclophosphamide is even suppressed in the same dose range.

Literature:

N. Brock: Pharmacological Principles of Cancer Chemotherapy In: A. Georgii (Ed.), Verhandlungen der Deutschen Krebsgesellschaft Volume 1, pp. 15-42, Gustav Fischer Publishers, Stuttgart (1978)

This curative and cytostatic action is comparable with the action of the known medicaments cyclophosphamide and ifosfamide. The lowest, readily curative or cytostatically active dose in the animal experiments indicated is, for example

0.01 mg/kg orally

0.01 mg/kg intraperitoneally

0.01 mg/kg intravenously.

A more generally suitable dose range for the curative and cytostatic action (animal experiment as above) is, for example:

0.01-100 mg/kg orally, in particular 0.1-10.0 mg/kg

0.01-100 mg/kg intraperitoneally, in particular 0.1-10.0 mg/kg

0.01-100 mg/kg intravenously, in particular 0.1-10.0 mg/kg

Possible indications for the compounds according to the invention may be: malignant diseases of humans and animals.

The pharmaceutical preparations in general contain between 1 mg to 1 g, preferably 100 to 1,000 mg, of the active component(s) according to the invention.

The administration may take place, for example, in the form of tablets, capsules, pills, coated tablets, suppositories, ointments, gels, creams, powders, dusting powders, aerosols or in liquid form. Suitable liquid use forms are, for example: oily or alcoholic or aqueous solutions and also suspensions and emulsions. Preferred use forms are tablets which contain between 10 and 200 mg or solutions which contain between 0.1 to 5% of active substance.

The individual dose of the active components according to the invention may be, for example

a) with oral medicament forms between 1-100 mg/kg, preferably 10-60 mg/kg,

b) with parenteral medicament forms (for example intravenous, intramuscular) between 1-100 mg/kg, preferably 10-60 mg/kg,

c) with medicament forms for rectal or vaginal administration between 1-100 mg/kg, preferably 10-60 mg/kg,

d) with medicament forms for local administration to the skin and mucous membranes (for example in the form of solutions, lotions, emulsions, ointments etc.) between 1-100 mg/kg, preferably 10-60 mg/kg.

- The doses are in each case related to the free base -

For example, 1 to 10 tablets containing 10 to 300 mg of active substance may be recommended 1-3 times daily or, for example, on intravenous injection one or more ampoules of 1 to 10 ml content containing 10 to 250 mg of substance 1 to 2 times daily. On oral administration the minimum daily dose is, for example, 200 mg; the maximum daily dose on oral administration should not be above 5,000 mg. A continuous infusion of suitable doses over 12 and more hours may also be recommended in individual cases.

For the treatment of dogs and cats, the oral individual dose is in general between about 10 and 60 mg/kg of body weight; the parenteral dose between about 10 and 60 mg/kg of body weight.

For the treatment of horses and cattle, the oral individual dose is in general between about 10 and 60 mg/kg of body weight; the parenteral individual dose between about 10 and 60 mg/kg of body weight.

The acute toxicity of the compounds according to the invention in the mouse (expressed by the LD 50 mg/kg; method according to Miller and Tainter: Proc. Soc. Exper. Biol. a. Med. 57 (1944) 261) is, for example, between 100 and 1,000 mg/kg (or above 1,000 mg/kg) on oral administration.

The medicaments can be used alone or admixed with other pharmacologically active substances in human medicine,

veterinary medicine and in agriculture.

Example 1

4-2-(Sulphoethylthio)cyclophosphamide* glycinamide salt

5 g (18 mmol) of 2-mercaptoethanesulphonic acid glycinamide salt in 40 ml of acetone are added to 4.0 g (18 mmol) of 4-hydroxycyclophosphamide in 10 ml of distilled water. The reaction solution is acidified to a pH of 4 using trichloroacetic acid, and kept for 2 hours at 5°C and 20 hours at -25°C. The salt precipitates as crystals and is filtered off with suction, washed, dried and recrystallized from water/acetone.

M.p. 90-98°C; yield: 7.2 g (76% of theory).

The salt contains about 1 equivalent of acetone.

Example 2

4-[1-Hydroxy-3-carboxymethyl-1-ureido]cyclophosphamide lysine salt (L-lysine)

7.5 g (24.6 mmol) of 4-ethoxycyclophosphamide and 3 g (22.4 mmol) of 1-hydroxy-3-carboxymethylurea are kept for 20 hours at 0°C in 50 ml of dry alcohol. The reaction solution is subsequently concentrated in vacuo at 20°C, the residue is taken up in 200 ml of acetone, 3.3 g (22.6 mmol) of L-lysine in 25 ml of methanol are added and the gelatinous precipitate is centrifuged after standing for a short time. The residue is dissolved in water, filtered, precipitated using acetone, filtered off with suction and washed with acetone/ether.

M.p. 125-128°C; yield: 6.5 g (54% of theory).

Example 3

4-(2-Sulphoethylthio)cyclophosphamide glycinamide salt

A solution of 3.1 g (6.5 mmol) of 4-(3-sulphopropylthio)cyclophosphamide guanidine salt and 4.2 g (19.6 mmol) of 2-mercaptoethanesulphonic acid glycine amide salt in 15 ml of water is adjusted to pH 7.5 using sodium hydroxide solution and warmed to about 40°C for 5 minutes. The reaction solution is subsequently cooled to

*Cyclophosphamide = 2-[2-(bis-(2-chloroethyl)amino)]-2-oxo-tetrahydro-2H-1,3,2-oxazaphosphorine

0°C and adjusted to pH 4.5 using sulphuric acid, 70 ml of acetone are added and the mixture is kept at 4°C for 3 days. The precipitate is filtered off with suction and recrystallized from water/acetone.

M.p. from 85°C (decomposition); yield: 430 mg (14% of theory).

Example 4

4-(2-Sulphoethylthio)cyclophosphamide arginine salt (L-arginine)

37.2 g (74.5 mmol) of 4-(2-sulphoethylthio)cyclophosphamide cyclohexylamine salt are dissolved in 320 ml of distilled water at 5°C (pH 4.3) and added over a column containing 150 ml of cation exchanger cooled to 4°C. A gel-like polystyrene resin containing 8% of divinylbenzene which contains sulphonic acid groups which are loaded with arginine is formed.

Flow rate: 6 ml/minute. Rinsed out using 250 ml of water. The eluate cooled to 4°C is diluted using cold water to give a 5% strength solution and is subsequently lyophilized.

M.p. 85-90°C (decomposition); yield: 42.9 g (100% of theory.

The addition of a buffer substance and/or a mercaptoalkylsulphonic acid can take place as follows:

a) Addition of sodium citrate buffer

The procedure is as indicated above, but the eluate is collected in sodium citrate buffer (pH 4.1) and diluted, for example, subsequently to give a solution which is 0.5 molar in sodium citrate and 5% strength in active compound. This is subsequently lyophilized. Yield: 42.9 g (100% of theory), of compound according to Example 4 containing sodium citrate buffer.

b) Addition of sodium citrate buffer and sodium 2-mercaptoethanesulphonate (mesna)

The procedure is as already indicated, but the eluate is collected in a cooled sodium citrate buffer solution (pH 4.1) which contains 8.2 g (50 mmol) of mesna and is subsequently lyophilized.

Yield: 42.9 g (100% of theory) of compound according

to Example 4 containing mesna and sodium citrate buffer.

Example 5

4-(2-Sulphoethylthio)cyclophosphamide lysine salt (L-lysine)

37.3 g (74.5 mmol) of 4-(2-sulphoethylthio)cyclophosphamide cyclohexylamine salt are eluted on an ion exchanger (protonated lysine form) analogously to Example 4 and are subsequently lyophilized.

M.p. from 85°C (decomposition); yield: 40.8 g (100% of theory).

A modified procedure is, for example, the following:

82.4 g (16.5 mmol) of 4-(2-sulphoethylthio)cyclophosphamide cyclohexylamine salt are dissolved in 850 ml of distilled water at 5°C. The solution is adjusted to pH 4.1 using several grains of strongly acidic ion exchanger (containing sulphonic acid groups) and added over a column containing 800 ml of ion exchanger* containing 820 mmol of sulphonic acid/L-lysine groups cooled to 4°C at a drop rate of 50 ml/minute. The first 180 ml of the eluate are rejected and the following eluate is continuously adjusted to pH 4.1 with stirring and ice water cooling using a total of about 1.5 ml of strongly acidic ion exchanger (containing sulphonic acid groups). The ion exchanger is rinsed out using 900 ml of distilled water cooled to 0°C. The eluate is subsequently diluted to give a 5% strength solution using cold water and is immediately lyophilized.

M.p. from 85°C, yield: 90 g (100% of theory).

Compound according to Example 5 containing lysine/citrate buffer (lysine + citric acid)

7.2 g (14.4 mmol) of 4-(2-sulphoethylthio)cyclophosphamide cyclohexylamine salt are dissolved in 80 ml of 0.05 M sodium citrate buffer (pH 4.1) at 4°C and added over a column containing 40 ml of cation exchanger resin (protonated lysine form) cooled to 4°C. The column is rinsed out using 80 ml of buffer solution, and the eluate is made up to 150 g of solution and lyophilized.

Yield: 7.9 g (100% of theory) of compound according to

*This is the same ion exchanger as in Example 4.

Example 5 containing lysine/citrate buffer.

Compound according to Example 5 containing 2-mercaptoethanesulphonic acid lysine salt and lysine/citrate buffer

7.2 g (14.4 mmol) of 4-(2-sulphoethylthio)cyclophosphamide cyclohexylamine salt and 1.5 g (9.2 mmol) of mesna are dissolved in 80 ml of 0.05 m sodium citrate buffer at pH 4.1 and are added over a column containing 40 ml of cation exchanger resin (protonated lysine form) cooled to 4°C. The column is rinsed out using 50 and 30 ml of buffer solution, and the cooled eluate is made up to 150 g of solution and lyophilized.

Yield: 7.9 g (100% of theory) of compound according to Example 5 containing 2.6 g (100% of theory) of 2-mercaptoethanesulphonic acid lysine salt and lysine citrate buffer (pH 4.1).

Example 6

4-(2-Sulphoethylthio)cyclophosphamide glycinamide salt

2.9 g (8.6 mmol) of 4-(2-hydroxyethylthio)cyclophosphamide and 5.6 g (26 mmol) of 2-mercaptoethanesulphonic acid glycinamide salt are dissolved in 35 ml of distilled water. The pH value is adjusted to about 8 using glycinamide. The reaction solution is warmed to about 40°C for about 4 minutes, then cooled to 0°C and, after the pH value has been lowered to about 4.5 by means of 2-mercaptoethanesulphonic acid, 500 ml of acetone are added. After several days at 4°C, the precipitate is filtered off with suction and recrystallized from water/acetone.

M.p. from 85°C

Yield: 410 mg (9% of theory)

The salt contains about 1 equivalent of acetone

Examples of pharmaceutical preparations

a) Example for the preparation of a lyophilizate of 4-sulphoethylthio cyclophosphamide lysine salt

90 g of 4-sulphoethylthio cyclophosphamide L-lysine salt are dissolved with stirring in 1,500 ml of water for injection cooled to 4°C. The solution is subsequently made up to 1,800 ml using water at 4°C. The pH is adjusted to about 4.2 using several grains of regenerated cation exchanger (H^+ form). To prepare the

the lyophilizate, the above solution is subjected to sterile filtration in a known manner. The collecting vessel is cooled. All the operations following sterile filtration are carried out under aseptic conditions. The sterile solution is made up to 2 ml in a 10 ml injection bottle. The active compound content is 100 mg.

The bottles are provided with sterile freeze-drying stoppers and are lyophilized in a freeze-drying unit. The unit is subsequently flushed with sterile, dried nitrogen and the ampoule bottles are closed in the unit. To prepare an injection solution which can be administered, the contents of the bottle are dissolved in 5 ml of water for injection.

The lyophilizate can be stored at 0-6°C (refrigerator).

b) Example of the preparation of a lyophilizate of 4-(2-sulphoethylthio)cyclophosphamide lysine salt (L-lysine) using citric acid/lysine buffer

1. An ion exchanger column having a cooling jacket is loaded with 1,300 ml of an acidic ion exchanger, regenerated using 2 litres of 10% strength hydrochloric acid and washed neutral and free of chloride ions using water for injection.
2. The column is subsequently loaded with the aid of 3 litres of a 10% strength lysine solution, freed from excess lysine by washing with water for injection and washed neutral.
3. 1.4 litres of a solution of the following composition are added over the column:

4-(sulphoethylthio)cyclophosphamide cyclohexylamine salt	137.12 g
citric acid, anhydrous	28.83 g
1 N NaOH	193.20 ml
water for injection	to 1.4 litres

Active compounds and auxiliaries are dissolved in water at about 4°C. The pH value of the solution is 4.1. The cation exchanger column is now also cooled to about 4°C. The above solution is added over the column. The flow rate is 10 ml/minute.

The eluate is collected in a cooled receiver, the first 300 ml being rejected as a forerun. The column is subsequently washed with water for injection cooled to 4°C and the total volume of the eluate is made up to 3 litres.

The eluate, which will be further processed to give lyophilizates, has the following composition:

4-(2-sulphoethylthio)cyclophosphamide lysine salt (L-lysine)	150.00 g
citric acid, anhydrous	28.83 g
L-lysine, anhydrous	28.24 g
water for injection	2870.93 g
	3078.00 g
	= 3,000 ml

4. To prepare the lyophilizate, the above solution is subjected to sterile filtration in a known manner. The collecting vessel is cooled. All the operations following the sterile filtration are carried out under aseptic conditions.

The sterile solution is filled into injection bottles as follows:

2 ml of solution in a 10 ml injection bottle
The active compound content is 100 mg

10 ml of solution in a 30 ml injection bottle
The active compound content is 500 mg

The bottles are provided with sterile freeze-drying stoppers and are lyophilized in a freeze-drying unit. The unit is subsequently flushed with sterile, dried nitrogen and the ampoule bottles are closed in the unit.

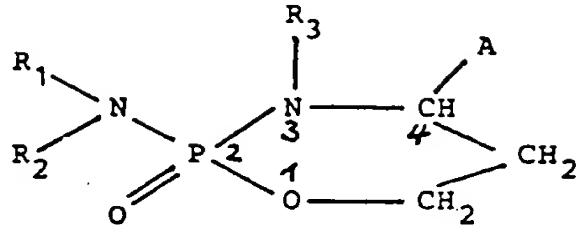
To prepare an injection solution which can be administered, the contents of the flask are dissolved in 5 ml of water for injection using 100 mg of active compound, or 25 ml of water for injection using 500 mg of active compound.

c) Example of the preparation of a lyophilizate 4-(sulphoethylthio)cyclophosphamide arginine salt

90 g of 4-(sulphoethylthio)cyclophosphamide arginine salt and 135 g of sodium 2-mercapto-ethanesulphonate are dissolved with stirring in 1,500 ml of water for injection, cooled to 4°C. After complete dissolution, the solution is made up to 1,800 ml with water of 4°C. The pH is adjusted to about 4.2 using several grains of regenerated cation exchanger (H^+ form). To prepare the lyophilizates, the above solution is subjected to sterile filtration in a known manner. The collecting vessel is cooled. All the operations following sterile filtration are carried out under aseptic conditions. 2 ml of sterile solution each time are filled into a 10 ml injection bottle. The active compound content is 100 mg. The bottles are provided with sterile freeze-drying stoppers and are lyophilized in a freeze-drying unit. The unit is subsequently flushed with sterile, dried nitrogen and the ampoule bottles are sealed in the unit. To prepare an injection solution which can be administered, the contents of the bottle are dissolved in 5 ml of water for injection.
The lyophilizate can be stored at 0 - 6°C (refrigerator).

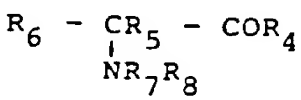
Patent claims:

1. Salts of oxazaphosphorine derivatives of the general formula



I

wherein R_1, R_2 and R_3, which can be identical or different from one another, represent hydrogen, methyl, ethyl, 2-chloroethyl or 2-methanesulphonyloxyethyl and in this case at least two of these radicals are 2-chloroethyl and/or 2-methanesulphonyloxyethyl and A is the group $-S-alk-SO_3H$ or $-N(OH)-CONH-alk-CO_2H$ and alk represents a C_2-C_6-alkylene radical optionally containing a mercapto group, where alk can also be $-CH_2-$ if the carboxyl group is on the group alk,
with homocysteine thiolactone or α-amino-ε-caprolactam or a basic compound of the formula

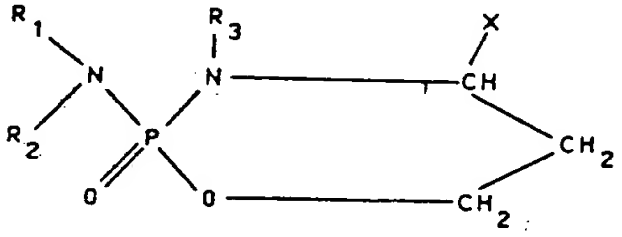


II

wherein R_4 is a hydroxyl group, an amino group or a C_1-C_6-alkoxy group, R_5 is hydrogen or a difluoromethyl group, R_6 denotes hydrogen, a 3-indolylmethyl radical, a 4-imidazolylmethyl radical, a C_1-C_{10}-alkyl group or a C_1-C_{10}-alkyl group which is substituted by a hydroxyl group, a C_1-C_6-alkoxy group, a mercapto group, a C_1-C_6-alkylthio group, a phenyl group, a hydroxyphenyl group, an amino-C_1-C_6-alkylthio group, an amino-C_1-C_6-alkyloxy group, an amino group, an aminocarbonyl group, a ureido group ($H_2NCONH-$), a guanidino group or a C_1-C_6-alkoxy-carbonyl group, or wherein R_6 together with the structural moiety $>CR_5(NR_7R_8)$ forms the proline radical, the 4-hydroxy-proline radical or the 2-oxo-3-amino-3-difluoromethylpiperidine and the radicals R_7 and R_8 represent hydrogen or C_1-C_6-alkyl radicals.

2. Salts according to Claim 1, characterized in that the basic compound is a compound of the formula II, wherein R_4 is a hydroxyl group or the amino group, the radicals R_5, R_7 and R_8 are hydrogen and R_6 denotes hydrogen or a C_1-C_4-alkyl group which, in particular in the ω-position, can be substituted by an amino group or a guanidino group.

3. Process for the preparation of salts of oxazaphosphorine derivatives of the general formula I according to Claim 1, characterized in that a compound of the general formula



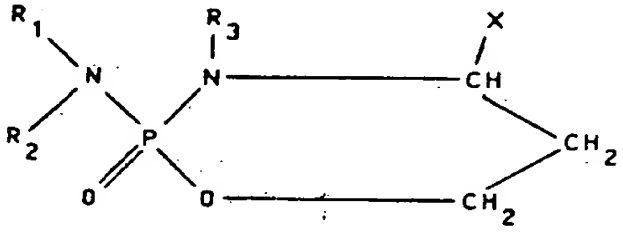
III

wherein X is a hydroxyl group or a C_1-C_4-alkoxy group, is reacted with the salt of the compound

AH IV

wherein A has the meanings indicated and the basic salt component is homocysteine thiolactone, α-amino-ε-caprolactam or the basic compound of the formula II having the meanings indicated for the radicals R_4 to R_8.

4. Process for the preparation of salts of oxazaphosphorine derivatives of the general formula I according to Claim 1, characterized in that a compound of the general formula



III

wherein X is a hydroxyl group or a C_1-C_4-alkoxy group, is first reacted with the compound

AH IV

and subsequently with homocysteine thiolactone, α-amino-ε-caprolactam or the basic compound of the formula II.

5. Process for the preparation of salts of oxazaphosphorine derivatives of the general formula I according to Claim 1, characterized in that a compound of the general formula III, wherein X is a C_1-C_{10}-alkyl-thio group which is optionally substituted by a carboxyl group, a hydroxyl group or a C_1-C_4-carbalkoxy group, a benzylthio group or a C_1-C_6-alkanoylthio group, or wherein X represents the group -N(OH)-CO-NHR and R denotes hydrogen, a C_1-C_6-alkyl group, a benzyl group or a phenyl group which is optionally substituted by C_1-C_4-alkyl radicals or halogen, or wherein X is the group A and the radical X can also be present in the salt form, is reacted with excess of a compound of the formula

A'H V

or a salt of this compound A'H or with homocysteine thiolactone, α-amino-ε-caprolactam or the basic compound of the formula II having the meanings indicated for the radicals R_4 to R_8, where A' is different from A and has one of the meanings indicated for A.

6. Process for the preparation of salts of oxazaphosphorine derivatives of the general formula I according to Claim 1, characterized in that a compound of the formula I or the salt of a compound of the general formula I is reacted with homocysteine thiolactone, α-amino-ε-caprolactam or a basic compound of the formula II having the meanings indicated for R_4 to R_8 or with their salts with the formation of the corresponding salts.

7. Process for the preparation of salts of oxazaphosphorine derivatives of the general formula I according to Claim 1, characterized in that the basic components or the acidic hydrogen of the group A, if this is not present as a salt, is exchanged for another basic compound in the context of the definition given therefor in compounds of the formula I.

8. Medicaments, containing a salt according to one or more of the foregoing claims in addition to customary excipients and/or diluents or auxiliaries.

9. Medicaments according to Claim 8, characterized

in that it additionally contains a buffer and/or the alkali metal salt of a mercapto-C_2-C_6-alkanesulphonic acid.

10. Process for the preparation of a medicament, characterized in that a compound according to Claim 1 or 2 is processed to give pharmaceutical preparations using customary pharmaceutical excipients or diluents or other auxiliaries, or is brought into a therapeutically utilizable form.

11. Process according to Claim 10, characterized in that buffer and/or the alkali metal salt of a mercapto-C_2-C_6-alkanesulphonic acid are additionally used.

12. Use of compounds according to Claim 1 or 2 for the preparation of medicaments.